



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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JAN 13 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Tribufos (DEF), rat metabolism study

TO: Cristine Rice PM-52
Reregistration Branch
Special Review and Reregistration Division (H7508C)

FROM: *[Signature]* 1/8/92
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THROUGH: Albin Kocialski Ph.D. *ABK*
Head
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William Burnam
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HED (H7509C)

Compound; Tribufos

Tox Chem #864

MRID #420345-01

Registration #074801

Registrant; Mobay

Tox Project #2-0181

Action Requested

Review the following study;

Disposition and metabolism of [1-¹⁴C] Tribufos in rats. L-R. M. Kao, R.N. Midden, L.L. Bosnal and M.E. Krolski; Mobay, Ag Chem Div, Research and Development Department, Study Number DE041801, Report Number 101331, Aug 28, 1991, MRID 420345-01

Core Classification Guideline

Conclusion

[1-¹⁴C] Tribufos 5 male and 5 female rats single oral dose, 5mg/kg or 100 mg/kg or 5 mg/kg/day X 14 days cold tribufos followed by 5 mg/kg [1-¹⁴C] Tribufos. 55 to 80 % absorbed. 90+% excreted in 72 hours. No significant tissue residue. Absorbed material extensively and completely metabolized.

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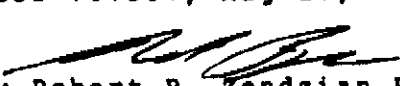
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Compound Tribufos (DEF)Citation

Disposition and metabolism of [1-¹⁴C] Tribufos in rats. L-R. M. Kao, R.N. Midden, L.L. Bosnal and M.E. Krolski; Mobay, Ag Chem Div, Research and Development Department, Study Number DE041801, Report Number 101331, Aug 28, 1991, MRID 420345-01

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Reviewed by Robert P. Zendzian Ph.D.
Senior Pharmacologist
Health Effects Division

Core Classification GuidelineConclusion

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Materials

Tribufos (S,S,S-Tributyl phosphorotrithioate)

[1-¹⁴C] labeled (adjacent to the S)
vial # C-422
specific activity 20.4 mCi/mmole
97% radiochemically pure

non-radioactive
vial # K-98
purity 100%

Radiolabeled material was diluted with nonradiolabeled material to yield a working solution with a specific activity of 2.04 mCi/mmole (14,400 dpm/ug).

Non-radioactive reference standards were either obtained from commercial suppliers or synthesized by the registrant. Reference compounds are presented in Figure 1 from the report.

Sprague-Dawley rats (approximately 200 gms each sex) from SASCO Inc. Omaha NE.

Preliminary experiment

To detect expired radiolabel, three rats of each sex were dosed orally with 5 mg/kg ¹⁴C-tribufos. Rats were placed individually in glass metabolism cages, for 72 hours, with the air outflow trapped to collect expired radiolabeled material. Urine and feces were also collected.

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Main Experiment

[¹⁴C]-Tribufos was dissolved in corn oil and administered by gavage. Rats were dosed as follows;

Group	Dose (mg/kg)		Number	
	Cold	¹⁴ -C	Males	Females
LDE		5	5	5
HDE		100	5	5
LDCE	5X14Ds	5	7 - 5	7 - 5

Treated rats were placed individually in plastic metabolism cages for 72 hours. Urine and feces were collected at 8, 24, 48 and 72 hours post dosing with radiolabel.

At 72 hours after dosing the rats were anesthetized with halothane and a blood sample taken from the heart. Bone, brain, fat, gonad, heart, kidney, liver, lung, muscle, spleen, gastrointestinal tract and residual carcass were collected for analysis. Organs were weighted and percent radioactivity determined. Percent radioactivity in blood, fat and muscle was estimated based on 8, 11 and 50% of body weight respectively.

Urine and fecal samples were analyzed for radioactivity and composite samples of each prepared for metabolite identification. Portions of the samples were hydrolyzed with sulfatase or B-glucuronidase. Metabolism samples were analyzed with an hplc system (Beckman System Gold, Fullerton CA).

Results

Recovery and distribution of radioactivity from the preliminary experiment is presented in Table 2 from the report. Ninety plus percent of radioactivity was excreted in urine and feces in 72 hours with no more than one percent in the air traps.

Results of the main experiment are presented in Tables 3, 4, 5, 6 and 7 from the report.

Distribution of radioactivity (Table 3) shows the majority of the radioactive dose excreted in urine and feces, with the females showing more in the urine than the males for each dose regimen. The portion of dose in the urine increases in the order LDE < HDE < LDCE for both sexes. This may be indicative of increased absorption and/or metabolism with dose.

Excretion with time is presented in Table 4. Excretion by either route was rapid, although they could not be calculated

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with the data available, half-times for excretion for both routes, both sexes and all dose regimens were considerably less than 24 hours.

The distribution of radioactivity and concentration in the tissues analyzed are presented in Tables 5 and 6. Only residual carcass in LDE and LDCE groups and liver in the male LDE groups showed 1 percent or more the radioactive dose retained at 72 hours. PPM values showed highest concentration in the metabolic and excretory organs, the liver and kidney. In these organs LDCE values were less than LDE values. This supports the excretion data in indicating that pretreatment with nonradiolabeled material increased the rate of metabolism and excretion of the radiolabeled dose.

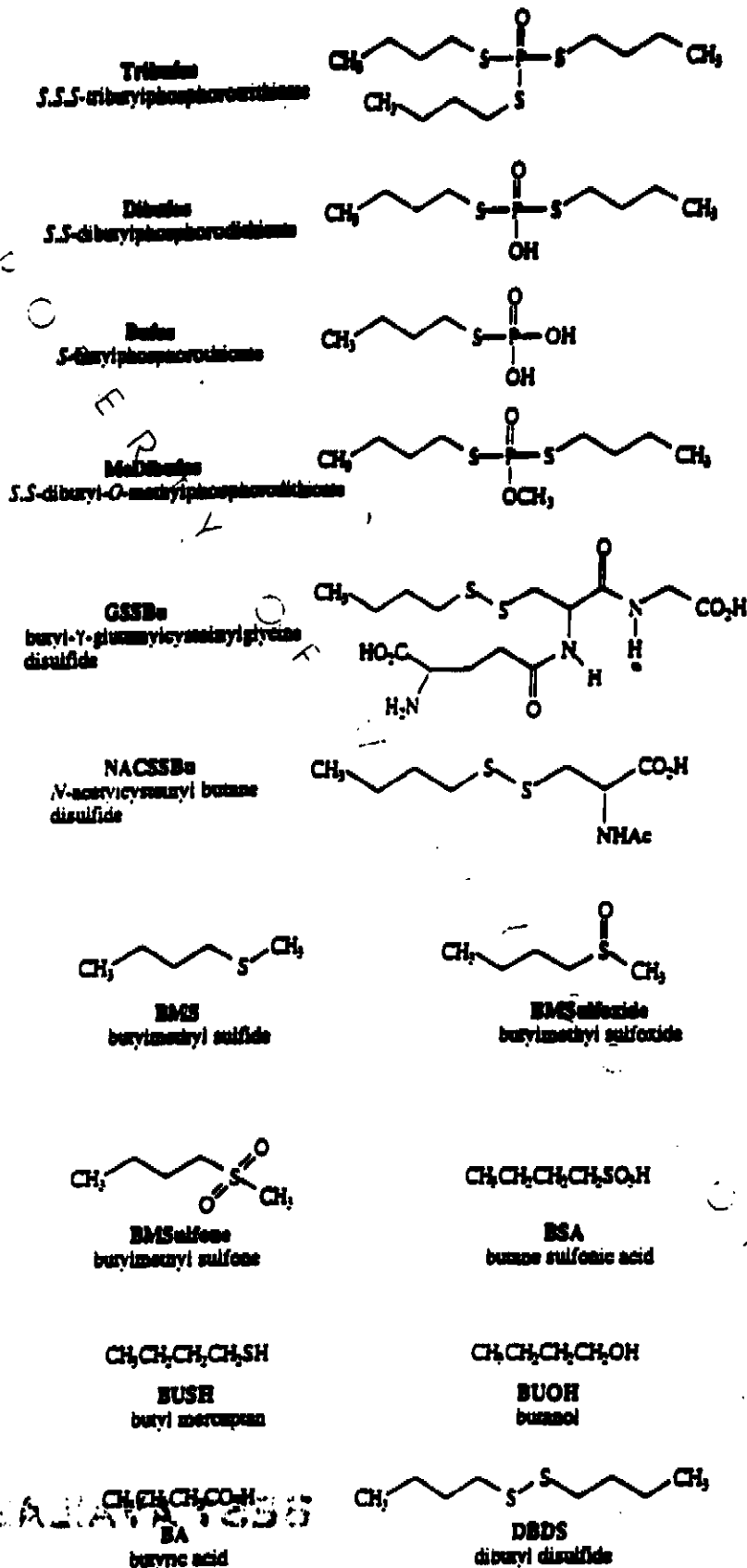
Metabolite identification data is presented in Table 7. Only two excreted compounds could be identified, unmetabolized tribufos in the feces and butyl-gamma-glutamylcysteinylglycine disulfide in the urine. The data indicate complete metabolic breakdown of absorbed tribufos with extensive breakdown of the S-butyl moieties probably to two carbon fractions. No evidence of sulfidation or glucuronidation was observed following treatment with sulfatase or B-glucuronidase.

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Figure 1. Chemical names and structures for tribufos and related standards.

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Table 2. Recovery and distribution of radioactivity from rats following a single oral dose of [$1-^{14}\text{C}$] tribufos at a rate of 5 mg/kg body weight (preliminary experiment).

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	Cumulative Percent Total Radioactivity			
	Hours Posttreatment			
	8	24	48	72
Male Rats				
Urine	25	62	67	68
Feces	0	18	21	21
1N KOH	NA	<1	<1	1
Glycol	NA	<1	<1	<1
Total	25	81	88	90
Female Rats				
Urine	0	62	68	70
Feces	0	17	25	25
1N KOH	NA	1	1	1
Glycol	NA	<1	<1	<1
Total	0	80	94	96

NA = Not Applicable. Traps were not sampled until 24 hours posttreatment.

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Table 3. Distribution of radioactivity among urine, feces, cage wash and tissues in the [¹⁴C] tribufos rat metabolism study.¹

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	Percent Total Dose					
	LDE		HDE		LDCE	
	Male	Female	Male	Female	Male	Female
Urine	55	66	60	70	73	80
Feces	42	30	38	27	24	15
Cage Wash	<1	<1	<1	1	1	2
Tissues	<u>3</u>	<u>3</u>	<u>2</u>	<u>2</u>	<u>2</u>	<u>3</u>
Total	100	100	100	100	100	100
Actual Recovery	101	95	94	97	90	90

¹LDE (low dose experiment, 5 mg/kg); HDE (high dose experiment, 100 mg/kg); LDCE (low dose chronic experiment, 5 mg/kg).

²Values were average of five rats for each dose group.

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Table 4. Excretion of radioactive residues from rats following treatment with [1-¹⁴C] tribufos.^{1,2}

Cumulative Percent Total Radioactivity					009008
Hours Posttreatment					
	8	24	48	72	
LDE					
Male Rats					
Urine	23	50	54	55	
Feces	N.A. ³	41	42	42	
Total	23	91	96	97	
Female Rats					
Urine	N.A.	62	66	66	
Feces	N.A.	25	30	30	
Total	N.A.	87	96	96	
HDE					
Male Rats					
Urine	N.A.	44	59	60	
Feces	N.A.	31	37	38	
Total	N.A.	75	86	98	
Female Rats					
Urine	N.A.	40	65	70	
Feces	N.A.	17	26	27	
Total	N.A.	57	91	97	
LDCE					
Male Rats					
Urine	28	67	72	73	
Feces	<1	22	24	24	
Total	28	89	96	97	
Female Rats					
Urine	N.A.	72	78	80	
Feces	N.A.	13	15	15	
Total	N.A.	85	93	95	

¹LDE (low dose experiment, 5 mg/kg); HDE (high dose experiment, 100 mg/kg); LDCE (low dose chronic experiment, 5 mg/kg).

²Values were average of five rats for each dose group.

³The excreta were not analyzed because most rats did not excrete urine or feces.

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Table 5. Distribution of radioactivity among various tissues in rats 72 hours after treatment with [¹⁴C] tribufos^{1,2}

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	Percent Recovered Radioactivity					
	LDE		HDE		LDCE	
	M	F	M	F	M	F
Blood ³	<1	<1	<1	<1	<1	<1
Bone	<1	<1	<1	<1	<1	<1
Brain	<1	<1	<1	<1	<1	<1
Fat	<1	<1	<1	<1	<1	<1
Gonads	<1	<1	<1	<1	<1	<1
Heart	<1	<1	<1	<1	<1	<1
Kidney	<1	<1	<1	<1	<1	<1
Liver	1	<1	<1	<1	<1	<1
Lung	<1	<1	<1	<1	<1	<1
Muscle	<1	<1	<1	<1	<1	<1
Spleen	<1	<1	<1	<1	<1	<1
GI Tract	<1	<1	<1	<1	<1	<1
Residual Carcass	2	2	<1	<1	1	2
Total	3	3	2	1	2	3

¹Values were average of five rats for each dose group.

²LDE (low dose experiment, 5 mg/kg); HDE (high dose experiment, 100 mg/kg); LDCE (low dose chronic experiment, 5 mg/kg).

³Blood, bone, fat and muscle were not totally excised. The percent of radioactivity shown was estimated based on 8, 11 and 50% of body weight for blood, fat and muscle, respectively.

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Table 6. Ppm values for radioactive residues remaining in rat tissues 72 hours after treatment of [^{14}C] tribufos^{1,2}

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	LDE		Ppm HDE		LDCE	
	M	F	M	F	M	F
Blood	0.129	0.191	1.855	2.342	0.141	0.137
Bone	0.071	0.080	1.007	0.861	0.072	0.060
Brain	0.023	0.045	0.841	0.707	0.045	0.046
Fat	0.413	0.152	1.931	1.773	0.205	0.122
Gonads	0.062	0.131	0.767	1.211	0.061	0.078
Heart	0.070	0.113	0.506	0.605	0.073	0.077
Kidney	0.216	0.272	2.460	3.133	0.240	0.258
Liver	1.078	1.306	5.951	7.653	0.735	0.685
Lung	0.265	0.287	1.875	2.484	0.171	0.175
Muscle	0.044	0.053	0.720	0.679	0.053	0.065
Spleen	0.088	0.159	1.659	2.159	0.112	0.131
GI Tract	0.090	0.104	1.228	1.676	0.158	0.158

¹The concentration of [^{14}C] tribufos-derived radioactivity in tissues is expressed as ppm (μg [^{14}C] tribufos/g tissue).

²LDE (low dose experiment, 5 mg/kg); HDE (high dose experiment, 100 mg/kg); LDCE (low dose chronic experiment, 5 mg/kg).

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Table 7. Distribution of radioactive residues among metabolites from composite fecal and urine samples obtained in the tribufos rat metabolism study.

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	Percent Recovered Radioactivity					
	LDE		HDE		LDCE	
	M	F	M	F	M	F
Feces						
Tribufos	28	20	31	22	23	15
F1	0	0	0	1	1	0
Urine						
U1	14	17	15	20	17	20
U2	3	6	6	8	4	9
U3	5	5	4	8	6	7
U4	3	5	4	5	5	5
U5	2	3	2	3	2	3
U6	3	4	3	3	5	6
U7	1	2	3	3	2	2
U8	2	2	1	3	3	2
U9	3	3	1	2	4	4
U10	4	3	3	2	4	4
U11	4	3	3	2	5	6
GSSBu	1	3	4	2	3	3
U13	3	2	2	2	2	2
U14	1	-	1	2	2	1
U15	2	1	1	2	2	2
U16	2	3	2	1	2	2
U17	1	2	3	1	2	1
U18	1	2	2	1	3	1
Total	83	86	91	82	97	95

END